healing, extrusion, pneumothorax, pregnancy or lactation difficulties for both augmentation and revision cohorts at three, six, and 12 months.

Now, if we look at these complications and place them in the context of those reported in the medical literature, we identify that, for instance, the reported frequency of hematoma and seroma in the literature is also higher.

Biggs in 1990 reported 1.4 percent. Artz in 1991 reported a 4.5 percent, and Gylbert in '89 reported as high as 20 percent incidence.

The frequency of the infection reported in the medical literature ranges from one to five percent. Crespo in '94 reported five percent, and Furey in '94 also reported 5.8 percent.

Identifying lactation difficulties which have been raised in the past as a concern, the prevalence of breast feeding problems in the general population is certainly not well defined. Few studies have evaluated women with silicone breast implants. These studies report that approximately 64 percent of women with implants may experience lactation

insufficiency compared to ten percent of women without implants.

This was reported by Hurst in '96, Neifert in 1990, and Strom in '97. These studies indicate that the relative risk of lactation insufficiency is at least three times greater in women who have a history of breast surgery, and the risk of lactation insufficiency increases with a periareolar incision. This was not seen in the PIP data.

As reported by Rees in 1980, prosthesis displacement is less likely to occur if accurate dissection of the packed pocket is carried out. In a subglandular placement of the implants, disruption of the fibrous attachments of the breast at the inframammary crease may result in inferior placement of the prosthesis. Implants placed behind the pectoral muscle are subject to superior and lateral displacement from the forces of contracture of the muscle.

In the PIP study, fold formation was assessed by study surgeons on physical exam. Fold formation is acknowledged in the literature, but

without distinct analysis being made correlating etiology to incidence. Mladick in 1993 showed that fold formation is partially dependent on surgeon's experience, anatomic placement, and change of implant design over the years.

Okay. One of the main reasons for patient dissatisfaction is failure of implants and in this case is deflation at any time during the patient's life span.

However, the NIH consensus statement on improving implant performance through retrieval of January 2000 acknowledge that, and I quote -- the quote refers generally to implants -- "Although implant devices have produced great benefits, it must be recognized that all medical implant devices are subject to failure."

Deflation has been reported hours to years after surgery. The release of saline from the device possesses no known risk to the patient, but leads to reoperation.

PIP reported values for deflation -- I'm sorry -- are one to four percent in the augmentation

cohort, being within the reported rates in the literature which range from one to 37.7 percent, as reported by Mladick in '93, or .5 to 20 percent as reported by Lavine in '93.

Change in nipple sensitivity. The PIP's reported frequency of nipple sensitivity, as you see, are 41 and 50 percent for augmentation and revision cohorts, respectively, at 12 months. These numbers are not surprising considering the damage to the sensory nerves of the breast and nipple at the time of surgery.

Permanent sensory changes of the nipple have been reported as 41 percent by Fiala in '93, while partial to complete sensory loss of the nipple was reported as high as 70 percent, and in the whole breast as 12 percent, and this was reported by Peters in '97.

A certain degree of breast asymmetry is present in most, if not all, women. This is consistent with the normal variation that exists in the two sides of the body. The incidence of significant mammary asymmetry is not known since many

women with the problem most likely never seek surgical correction.

Pitanguy in '74 reported noticeable asymmetry in four percent of 1,273 patients undergoing mammoplasty, but the incidence in the general population is believed to be higher, as indicated by Rees in 1980.

This data reflects the anticipated postoperative course with most of the swelling and inflammation being present in the first three months, followed by a decline at six months and one year postoperatively as nephatic drainage improves.

We will now evaluate these complications in a different context, and that has to do with the type of implant, meaning textured versus smooth, and placement, and that has to do with retropectoral versus subglandular placement.

We will first look at the augmentation cohort where textured implant in a retropectoral position was placed. I'm sorry. These next few slides are rather busy, and I will try to summarize them as we move along.

Next we will be looking at the textured subglandular placement, and again, these are the incidences that you see. Now, there was a zero incidence of hematoma, seroma, infection, delayed healing, extrusion, folds, deflation, asymmetry, pneumothorax, pregnancy, and lactation difficulties at three, six, and 12 months, and this was reported for the textured, subglandular, and retropectoral implants.

Now, for the revision cohort, again, we look at the same criteria, textured retropectoral and textured subglandular, and for this cohort there was zero incidence of hematoma, seroma, infection, delayed healing, extrusion, deflation, pregnancy and lactation difficulties at three, six, and 12 months.

To summarize this last few slides and specifically to look at the capsular contracture, since this represents one of the most severe complications, for the augmentation and revision cohorts, there was zero incidence of capsular contracture Grade III and IV for textured implants placed retropectorally and subglandularly.

And I'm sorry we have to go through this exercise once more, this time looking at augmentation cohort with smooth implants placed retropectorally and smooth implants placed subglandularly, and here we report zero percent of hematoma, seroma, infection, delayed healing, displacement, extrusion, and so on and so forth, at three, six, and 12 months.

For the revision cohorts again with the smooth implants in those two placements, these are the complications, and in the subglandular position, these are the complications.

And again, to conclude for you, there was zero incidence of hematoma, seroma, infection, and the rest at three, six, and 12 months.

Again, to conclude these last few slides and once again to focus on capsular contracture, for the augmentation cohort this was four percent or one in 24 patients who developed a capsular contracture Grade IV for smooth retropectoral implantation at six months, and 17 percent or one out of six patients who developed capsular contracture Grade III for smooth subglandular implantation at six months.

There was zero incidence of capsular contracture for the revision cohort with smooth implants used in either placement.

We will move on and look at -- okay. In the PIP study for the augmentation cohort, the cumulative frequency distribution of events resulting in additional surgery at each scheduled follow-up visit is one to two percent, while for revision is zero percent.

These values are lower than those reported in the medical literature. In fact, local complications are relatively common with this kind of surgery. Gabriel in '97 reported of the 749 implanted patients, 24 percent had at least one local complication and 19 percent of 1,454 implanted breasts required additional surgery.

Interestingly, the degree of satisfaction with the final outcome was equivalent for patients requiring a secondary procedure compared to those that did not, as reported by Strom in '97.

Our study also evaluated the possibility of development of connective tissue disease in study

patients. Connective tissue disorders represent a constellation of very complex and at times not well defined diseases.

Possible association between silicone breast implants and the development of rheumatic disorders was raised in the early 1980s. Placed into perspective is the fact that rheumatic diseases occur in the general population. One commonly performed laboratory test, for instance, the screen for connective tissue disease, is the presence of ANAs. This represents the most sensitive laboratory test for detecting lupus, but with low specificity as described by Wallace in 1989.

It has been determined that gender and age affect the prevalence of ANAs in the normal population. Women are found to be more commonly ANA positive than men, as described by Thomas and Robinson in '93, and the prevalence of ANAs increases with age as described by Slater in '96.

The IOM report of June '99 made an important distinction in that a positive ANA test is not a disease diagnosis.

As to the incidence of connective tissue disease in the general population, it is estimated that rheumatoid arthritis occurs in approximately one to two percent of the population, while lupus and scleroderma occur with a frequency of 143 and 113 per 100,000, respectively, as reported by Blackburn in '97.

An association of breast implants with autoimmune disease has been postulated, but causation has not been shown. The American College of Rheumatology declared at its 1995 national meeting that, I quote, "The American College of Rheumatology believes that these studies provide compelling evidence that silicone implants expose patients to no demonstrable additional risk of connective tissue or rheumatic diseases."

In the PIP study, the possibility of connective tissue disease was evaluated in 129 patients that had screening questionnaires at follow-up visits. The protocol identified these following connective tissue diseases.

The screening questionnaire was comprised

of 35 signs and 44 symptoms, possibly indicative of a particular disease, but I would like you to keep in mind that making the diagnosis of specific connective tissue disorder takes into account numerous variables, some of which are past medical history, complaints, findings on physical exam, and laboratory test results.

In the PIP study, the following symptoms were reported and the examining physicians identified only for signs. None of the patients were referred for further rheumatologic work-up. No significant association of these outcomes with the implant was identified by a paired comparison of baseline symptoms and postoperative reports of symptoms possibly related to connective tissue disease.

I would like to summarize for you briefly this clinical study where most of the reported complications in the cohorts were rare, but still within the range of medical literature reported incidences.

PIP also went on to further evaluate women in the context of quality of life. The efficacy of a

breast implant is assessed based on the implant's ability to enhance breast size, and in doing so, to improve a woman's self-esteem and quality of life.

Quality of life in our case and protocol was evaluated through these three different studies. In the PIP data, there is substantial variation from one quality of life measure to another. The largest and the most significant change is seen for sexual attractiveness with a mean increase of 4.6 points on the zero to 100 range, from baseline to three months.

This change has a P value, as you see of 0.0001.

The PIP have identified statistically significant and sometimes moderately strong associations between breast implant surgery and subsequent quality of life, as also reported in the medical literature.

Two measurements are associated with bust size: the circumference of the chest below the breast and the larger circumference of the bust measured at the nipples.

The key measurement of implant efficacy is

success in enhancing bust size, especially for the primary augmentation cohort. Revision may not be necessarily done for augmentation. Therefore, increase in bust size is not necessarily expected for this cohort.

In the primary augmentation cohort, baseline cup size was available for 324 patients out of 327 subjects with implants. Preoperative mode and median were both size B. At the end of the study, 159 cup sizes were available for this group, with size C as both the mode and median.

PIP effectiveness data demonstrates that in the augmentation cohort where increase in bust size is anticipated, mean and median increase was two plus or minus 1.3 inches. The distribution of cup size change is highly significant from pre to post implant in the augmentation cohort. The median change is an increase of 1.5 sizes, with a 95 percent confidence interval.

Mean change in the revision cohort where increased was not expected was an increase of .8 plus or minus 1.4 inches, with a median increase of zero.

For pooled cohorts, mode and median were both size B at baseline and size C at the end of the study with one cup size modal and median increase.

Lastly, I would like to share with you the U.S. surgeon case experience survey. PIP estimates that approximately 35,000 implants have been used in non-study patients in the United States since 1996. A survey of surgeons using PIP implants was initiated to access the status of patients and implants at two or more years postoperatively.

In 1997, PIP contracted with a third party to develop a database founded on PIP's medical device registration forms. According to this data, 3,480 patients have been implanted with this device who are now two or more years postoperative.

For the survey, 32 surgeons were identified that had 20 or more patients, for a total number of patients of 2,618. Twenty-two surgeons agreed to participate in a survey for a total number of patients of 1,257. Fifteen surgeons with a total number of 777 actually responded to the survey.

As I already stated, there was no overlap

of respondents in the survey and the patients in the clinical study. The respondents range in age between 18 to 50 with a fairly even distribution.

Approximately 86 percent, or 666 patients, were implanted for augmentation and 9.4 percent or 73 patients were implanted for revision.

The survey evaluated complications at one and two years as you see in this table, and essentially the data from the survey concurred the findings of the clinical study and overall demonstrate lower incidences of complications than those reported in the medical literature.

The survey also evaluated patient satisfaction, and four categories were allocated, as you see here, with subtotals for the satisfied and extremely satisfied, 4.8 percent, and those satisfied and extremely satisfied were 88.5 percent or -- and I cannot see from here -- I think 666 patients.

Therefore, 88.5 percent patients surveyed were satisfied, were extremely satisfied with their final results. This information is supported by published studies demonstrating satisfaction levels

for patients with all types of implants.

For instance, a survey conducted by Strom in '97 of 292 patients showed that 64 percent were satisfied with the augmentation;, 58 percent said they would recommend the procedure to others; 46 percent said the breast surgery improved their quality of life; and 51 percent stated that the implants improved their sexual attractiveness.

Overall postoperative satisfaction was rated as high by 74 percent, moderate by 15 percent, and low by 11 percent of patients in a study conducted by Fiala in 1993.

This essentially concludes my presentation of U.S. clinical study and survey through which safety and effectiveness have been demonstrated, and now I would like to introduce Dr. Jefferson Goudeau, who is from Lyon, France, and he will be presented the French data.

Thank you for your attention.

DR. GOUDEAU: Mr. Chairman, distinguished members of the panel, thank you for receiving me here today.

My name is Morgan Jefferson Goudeau. I was born in the United States in 1953. I graduated from Lyons Medical School, University in 1983. I'm a qualified plastic, reconstructive, and aesthetic surgeon with a private practice for 16 years in Lyons, France.

I am also a teaching doctor at the University Hospital. That is within the Great Berne Center, and a member of diverse professional societies.

I have no particular ties with PIP besides being a user of prefilled saline implants. Plus the trip was paid by the society.

The purpose of the French clinical study is to evaluate the rate of complications that occur six months, one year, and two years after the implantation of PIP's prefilled saline, textured implants and appreciate the safety and effectiveness of the procedure.

The protocol was set in 1995. It is a prospective study, and the implantations took place between 1995 and 1997. The follow-ups is 24 months,

and the study period ended on October 15, 1999.

The implant used in the French study is only the PIP's designed valveless, saline, prefilled, textured breast implant. That is why the complications rate is studied per indication and location and not per device.

The study carries 521 patients with 406 augmentations, 29 revisions, and 86 reconstructions done by six qualified plastic surgeons in France, including myself with 160 cases.

The indication for the use of the implants are breast augmentation, 406 patients out of the 521, which makes 78 percent; revision surgery, 29 patients out of the 521, which makes 5.5 percent; and reconstruction, 86 cases of the 521 patients, which makes 16.5 percent.

In the study the devices were implanted in the retropectoral position. The submuscular placement represents 82 percent of the cases versus 18 percent for the subglandular placements.

If we look more precisely into this, we see that in breast augmentation almost 80 percent of

the implants are in the retropectoral location. That's 322 patients out of 406, which makes 79.3 percent, and 20.7 percent of subglandular.

In reconstructive surgery, the retropectoral location jumps up to 96.5 percent, which is 83 patients out of 86, versus 3.5 percent in the subglandular position, if I say so.

In revision surgery, 24 cases out of the 29 are retropectoral, which gives 82.8 percent, and 17.2 percent of subglandular. As we can see, the retromuscular placement of the devices are in favor in our study, 82 percent versus 18.

We do feel that a deeper positioning of the implant gives a more natural result. We also do know that the interface prosthesis and muscular aponeurosis tissue generates a center capsule and less retraction than the interface breast tissue with the device, though less contracture.

In the reconstruction theory of 86 cases, the ratio, 96.5 percent versus 3.5 percent, is easily explainable by the necessity of a quality tissue coverage to prevent major inflammatory reaction and

extrusion of the implant in this adverse surrounding, that is, adjuvant, radio and chemotherapy, of course.

The type of surgical incision in our study depends on the indication, augmentation, revision, and reconstruction. The surgeon's skills are expertise, and the management of future expectable adverse reactions due to the approach. Sorry. That's nipple sensitivity, troubled lactation, radiology co-surveillance of the breast.

I'm personally in favor of the axillary approach, preserving lateral sensory nerves and lymphatic vessels. In our study, the data shows that axillary approach is 63 percent, periareolar approach 26, through preexisting incision ten percent, and inframammary approach one percent.

Slide, please. Thank you.

In the French study the overall follow-up status on a 24 month period shows an 80.9 percent rate, 426 patients out of the 521. This could be explained by the facts that France is a small country, and the population is not as mobile as in the United States.

Although the PIP's devices are marked, they have the brand, the volume, and the serial number on the patch. So in case of a revision made by another surgeon, the implant returns to PIP, who keeps the traceability and informs the former surgeon. That way the patient's data are back in the study. That's what happens in France when these cases come out.

If we look at the follow-up total status, we see 100 percent at six months, regardless of the indication, but at two years it drops to 81.9 percent.

In the revision cases, 45 percent at two years is a very low percentage. That could be explained by the small amount of cases, 29, which makes it statistically discussable.

On the other hand, the best rate of follow-ups at two years is in the augmentation cases, which is 87 percent, and we know that the highest rate of satisfaction is in this group. Nevertheless we still feel that if a patient doesn't show up to the consultation, that probably means that she is satisfied.

The contraindications arises similar in

France as in the United States: existing carcinoma of the breast, advanced fibrocystic disease, insufficient soft tissue coverage, unsuitable mental status, preexisting connective tissue disease, AIDs or HIV-plus with a low grade of T4 lymphocytes.

Existing carcinoma in the transfibrocystic diseases are ruled out with systematic preoperative mammographs and echograms. Insufficient soft tissue coverage and unsuitable mental status is left to the surgeon appreciation.

Preexisting connective tissue disease and AIDS are ruled out with systematic preoperative blood tests.

The mammary augmentation surgery investigation. The 406 cases of augmentation were mainly hypotrophy, 91.9 percent; mammary involution, 5.2 percent; and hypotrophy and mild, very mild, ptosis, 2.9 percent.

The age group mainly ranges from 25 to 35 years old in the augmentation cases.

Safety and effectiveness. The French study focused on the following surgical complication:

deflation, capsular contraction, Stage III and IV in regard o Baker's classification, infection, folds, asymmetry, and nipple sensitivity disorder.

We had six cases of hematoma out of the 406 patients, which is 1.5 percent or 1.7 percent if we considered percentage on the remained patients at two years, which s 253 and 406 patients.

We have two columns on our slides because we couldn't evaluate the correct data at two years with the loss in follow-ups. Though the complication cases are reported in Columna 1, referring to the initial number of patients, it's seven cases out of 406, but Column 2 shows that we manage the percentage regarding to the left patients at two years, which is 353.

The rate of deflation, which I will take the Column 2, the worst case. Two percent at two years' follow-up and infection 0.3 percent seems very low. I think this is mainly due to the valveless prefilled implant. The manipulation of the device is limited to a minimum, though it reduces the infection risk and the operation time.

The capsular contracted rate, Bakers III and IV together, represent a 1.4 percent. It's similar to any saline filled device, and much lower than silicone gel implants.

The high rate of asymmetry, 4.5 percent, is due mainly to the fact that the implant is generally in 79.6 percent of the cases in the submuscular position, and though it is more difficult to insure the stability of the implant in its pocket, especially in the inframammary region.

Another reason could be oversized prosthesis, but it is generally not the case in France. The nipple sensitivity problem, 1.4 percent, seems to be in relation with the approach used by the surgeon.

Revision. The type of implant revised with PIP's prefilled, valveless, saline implant shows a high rate of silicone gel implant. It's 62.1 percent. Hydrogel and saline comes behind, with respectively, 27.6 and 10.3 percent.

I would like to make a remark at this point. When a surgeon deals with a ruptured silicone

gel implant, the procedure is much more complicated. The ablation of the prosthesis, capsulectomy, and sometimes partial mastectomy in account of the silicone in those silicone gel infiltrated the breast tissue.

The disappointment and the frustration is high because you are bringing the patient from a cosmetic procedure to a reconstruction one, and the results are not the same. Of course, it's not the case with hydrogel or saline prosthesis revision.

Reconstruction. As in any studies, the complication rate is higher in reconstruction due mainly to the adverse environment encountered in these cases. Capsular contracture III and IV are almost four times higher than in augmentation. It's 6.6 percent versus 1.4 percent. Asymmetry, 11.5 percent versus 4.5 percent, while the inflation rate due to the implant is quite similar, 1.6 percent in reconstructive versus two percent in augmentation.

The total. If we look at the total percentage rate of adverse reaction referring to the three situations, augmentation, revision, and

reconstruction, and what is due to the implant: deflation, 2.1 percent; folds, 5.4 percent; and the surgeon, asymmetry, 6.3; nipple sensitivity, 2.1, we can see that the overall data are rather low and can lead to a very high level of patient satisfaction.

It seems that the patient satisfaction level is met in the study. In France, satisfied and very satisfied represent 97.8 percent, while fairly and slightly satisfied, 2.2 percent.

It seems in this 24 month follow-up study that we came out with no major complication. However, we have to keep in mind that the fight goes on that we as surgeons feel much more comfortable with saline prefilled implants than we do think that out-patients now have a choice.

Thank you for your attention and patience.

DR. CARABIN: And I would like to take a few more moments of your time to conclude this presentation.

The basis for approval of a medical device is safety and effectiveness. PIP prefilled saline breast implants have a demonstrable history of safe

and effective use in the United States, marketed under a 510(k) since 1996, for a total 35,000 implants.

The implant, unlike others, is prefilled and valveless. Indications for the use of the implant are augmentation and revision.

The safety of the implant was assessed through a multitude of preclinical and clinical studies as presented to you this afternoon. The preclinical studies showed no evidence of in vivo or in vitro toxicity, therefore demonstrating safety of the implant.

The clinical data was comprised of three separate studies: the U.S. study of 392 patients, the U.S. surgeon case experience survey of 777 patients, the two year prospective French study of 521 patients with a total of 1,690 patients.

We also have to consider the marketing experience and the number of MDRs of 521 or 1.48 percent out of 35,000 implants.

Complications that speak to the safety of breast implants are those that require further and significant medical or surgical intervention and alter

the desired cosmetic outcome.

Complications from breast implantation have various etiologies, fully identified in the medical literature and evaluated by PIPs clinical studies.

First, the U.S. study, most of the reported complications in a cohorts were rare, were changes in nipple sensitivity and asymmetry being more common, but still within the ranges of medical literature reported incidences.

There is zero percent incidence of hematoma, seroma, delayed health, extrusion, pneumothorax, pregnancy or lactation difficulty. Study patients showed no evidence of connective tissue disease.

Second, the U.S. surgeon case experience survey of 777 patients two or more years postoperatively concurred with the findings of the clinical study. The two year prospective French study of 521 patients also show rare complications with the most common being reported as asymmetry, fold formation, and nipple sensitivity, incidences that

remain below those reported in the medical literature.

PIP clinical data clearly shows safety of the implant, identifying incidences of complications well within the range of those reported in the medical literature.

Effectiveness. The efficacy of a breast implant is assessed based on the implant's ability to enhance bust size and in doing so, to improve a woman's self-esteem and quality of life. In the U.S. study, PIP demonstrated an increase in breast size. For quality of life, the most significant finding was increase in perceived sexual attractiveness at three and six months.

The U.S. surgeon case experience survey demonstrated an 88.5 percent satisfaction of patients with their end results, and the French study showed that 97.8 percent of patients were satisfied or extremely satisfied with their final results.

These three studies demonstrate the effectiveness of the implant and increased satisfaction on the part of patients.

This concludes PIP's PMA presentation to

the panel. However, I would like to leave you with one final conclusion. PIP's prefilled saline implants are safe and effective.

Thank you for your time.

CHAIRMAN WHALEN: Thank you. Are there questions of this panel for the sponsor?

Dr. Burkhardt.

DR.BURKHARDT: As I'm sure you know, plastic surgeons in this country had a very adverse experience about 15 years ago with an implant whose shell at least appears to be the same general type of external shell that is used on the PIP implant.

Could you say a few words about the structure of the shell and why you think it is different from what we've experienced before?

MR. HAWK: Yes, sir, Dr. Burkhardt.

First, I'd like to say I have an extensive team of specialists behind me who will be answering certain questions.

DR. BURKHARDT: I will just defer that then.

MR. HAWK: And as they get up, they will

refer to who they are and where they're affiliated with.

DR. COVENEY: Good afternoon. Just to introduce myself, my name is Donal Coveney. I have a Ph.D. in organic chemistry from the University College, Dublin, Ireland, and I have five years' experience in the manufacture and testing of silicone materials for use in breast implants and am currently a tactical consultant for the medical device and pharmaceutical industries.

Just to address your question on this platinum cured elastomer material that PIP are using in the saline prefilled breast implant, it's a conventional polydimethylsiloxane silicone elastomer. It's a widely used material in a variety of other applications. For example, a lot of the other manufacturers would use this material in their silicone gel filled implant shells.

Just to clarify, the competitors are using what I would classify a tin cured silicone elastomer, where PIP are using a platinum cured silicone elastomer. As I say, they're both silicone

elastomers. They're both well established and characterized materials.

Both of these materials will cure at room temperature. It's simply a matter of cure rate. There is some marketing difference of opinion. Tin cured is sometimes typically called RTV and platinum HTV, but in actual fact, both materials will cure at room temperature. This is just simply a matter of rate of cure.

Both materials are actually cured at an elevated temperature in the actual processing of the materials. We would perceive there are some advantages, in fact, to the platinum cured material. The physical properties of both elastomers are extremely similar. One slight difference would be that the elongation of the platinum cured material is actually slightly improved, and we would certainly perceive that as an advantage.

In addition, the platinum cured material has a much lower metal content. The platinum level is typically five parts per million or less as standard tin cured materials would be considerably higher than

that, although I'm not here to discuss that material obviously, but I do so for comparison sake.

In addition, the platinum cured material doesn't have a byproduct. The tin cured material has acetic acid, you know, the typical vinegar smell in bathroom caulk, for example, that I think everybody knows and is familiar with. So obviously that's something that has to be addressed in curing the tin material.

I think, just apart from the chemical characteristics of the material, that the clinical data supports the reliability of this platinum cured elastomer, and I think the rupture rates, as explained by my colleagues, speak for themselves.

Does that answer your question?

DR. BURKHARDT: Well, yes it does. I'm not sure how satisfactorily. My overriding concern is that the one prosthesis with which we appear to have had comparable experience essentially had a 100 percent deflation rate and resulted in great difficulties in this country.

I'm very anxious to hear. I can't hold

you to another standard for an implant that you don't know about.

DR. COVENEY: Sure.

DR. BURKHARDT: But those of us who are older in plastic surgery remember this experience.

DR. COVENEY: I'm familiar with the anecdotal evidence.

DR. BURKHARDT: What's the difference between yours and theirs.

DR. COVENEY: My understanding from that product you're referring to is that that particular device had a very thin shell, and I think rupture was a problem with that device not so much because of the material of construction, but of the design of the device.

It also was a valved implant, which is another variable in the equation, if you like. I think that's -- lost my train of thought. Sorry.

DR. BURKHARDT: Thank you very much.

DR. COVENEY: Well, I think, no, I just remember the point I was about to make when my colleague interrupted me.

The point I was going to make was because of this problem with that implant and the market perceived this as a platinum cured problem, which I don't think that is the issue at all; it was the design of the device itself, and not the material of construction.

DR. BURKHARDT: And how is the design, aside from the valve -- we just don't want this to happen to us again -- aside from the lack of a valve, how is the design different?

DR. COVENEY: Well, the design --

DR. BURKHARDT: I mean you have a thicker shell, you say?

DR. COVENEY: Yeah. As I say, the anecdotal evidence of this particular product you're referring to is that it has a very thin shell. I mean that's all I can say about that product. I'm not more familiar with it. Perhaps some of my colleagues can answer in greater detail.

But as I say, historically people associated that problem with a platinum cured elastomer, which I think was a mistaken conclusion.

I think we have to rely on the clinical evidence for supports --

DR. BURKHARDT: Thank you.

DR. COVENEY: -- apart from that.

CHAIRMAN WHALEN: Dr. Chang.

DR. CHANG: Just as a corollary, could you tell us what is the range of thickness of the PIP product?

DR. COVENEY: I think I will pass over to the chairman.

DR. CHANG: Range of thickness.

MR. HAWK: It's 4.5 thickness on the shell on a PIP implant.

DR. CHANG: Millimeters or is that --

MR. HAWK: Millimeters, yes.

DR. CHANG: So that's about .022 inches? This thickness is 4.5 millimeters.

MR. HAWK: Yes, ma'am.

DR. LI: Just as a corollary, what's the range on that? Are you telling us everyone is exactly 4.5 millimeters?

MR. HAWK: No, I'm not. Let me find out

the range on that.

DR. CHANG: I have a clinical question for either of our physicians. The rate of wrinkling varied. I think the average for the last one, for the French study was four percent, but it was as high as 38 percent for revision, in one of the charts for the revision of the, I believe, prospective study.

Any reason for the percentage of wrinkling that you can conjecture?

And secondly, were any of the failed devices examined, and was the failure location related at all to wrinkling, as has been previously attested to in other studies?

DR. GOUDEAU: The revision case in France are total failure of the prosthesis because when the patient, which is generally skinny, sees the wrinkles on the side, it doesn't lead to -- I mean, in my experience. Maybe a younger surgeon might be more entitled to do a revision when the patient argues about a few little wrinkles, especially if he had the prosthesis under the gland.

In my case, I just describe that it's not

really an adverse event, and that to a certain extent, of course, because the normal breast of the same size will not be regular either.

So it depends really on who's the surgeon and how important the wrinkles are, but in the cases of revision in the French study, it was total deflation.

DR. CHANG: And then a corollary. Was there any --

DR. GOUDEAU: I'm not sure I understood the question right, but does that answer? Because I'm not sure I understood the question.

DR. CHANG: Why the rate of wrinkling. Why was wrinkling seen?

DR. GOUDEAU: It was seen by the patient when she was leaning forward in most of the cases, and sometimes she was feeling the wrinkles, and then she was worried because she thought it was something like cancer or whatever. So she would come back to the surgeon, and we reassured the patient that it was normal and it was just the prosthesis.

DR. CARABIN: If I may be allowed to

clarify, thank you.

I think one of the concerns you may have is possibly the different rates of reported folds in the U.S. versus French study, and I think that as I discussed with Dr. Goudeau, it certainly appears a lot has to do with technique.

In France, the preferred placement for the device is retropectorally, which certainly will allow for less perception of a wrinkle formation as opposed to the United States where the preferred placement is still subglandularly.

Also, in our study -- and I tried to clarify that during the presentation -- fold formation was assessed either by the physician at the time of examination or by the patient. Fold formation was not the equivalent of explantation, and our study in the United States reported seven explantations, and right now I'm trying to get for you the number of which were due to fold formation. I believe was two or three, but I do not want to give you the wrong information at this point. If you'll allow me some time, I'll be happy to research it.

Thank you.

CHAIRMAN WHALEN: Dr. Burkhardt.

DR. BURKHARDT: This is an unusual request, but do you just happen to have one of these things with you that we could look at?

MR. HAWK: We do not.

DR. BURKHARDT: Thank you.

DR. CARABIN: But we'll be happy to send you one.

(Laughter.)

CHAIRMAN WHALEN: Dr. Boykin.

DR. BOYKIN: Yeah, just to get back to the U.S. data that you had shown us earlier, and maybe I'm wrong, but it looks like when you were reviewing the 12 month experience, we noticed that you had significantly reduced follow-up, I think it was down to about 27 percent for the group, but what struck me also was that for asymmetry, nipple sensation or change in nipple sensation, and inflammation, the denominators were all different for the augmentation and reconstruction group at 12 months.

Could you go back to those slides and

let's look at it?

DR. CARABIN: Yeah, I'll be happy to do that.

If you'll give us just one second to get organized and find a --

DR. MUENZ: I'm Larry Muenz, and I'm the study statistician. I'm a consultant to AAC Group, which in turn is a consultant to PIP. I don't have any travel expenses since I came all the way from Gaithersburg.

(Laughter.)

DR. MUENZ: It's true the denominators are different, somewhat different, because different numbers of persons have a response at each time point. There's missing data. Not every item on every form is filled out. So it's correct. The denominators do differ somewhat.

Could you indicate -- let's see. Let me know, please, when you're at the one that makes you anxious.

DR. BOYKIN: You can start right there. Twelve months, change in nipple sensitivity, 19

percent for augmentation, 20 percent for revision, and you've got 54 patients that you've seen in the augmentation group.

DR. MUENZ: Yeah, that's 54 who responded to that particular item. There is a response negative or positive for that item.

DR. BOYKIN: For that item?

DR. MUENZ: Right.

MS. DUBLER: So these are self-administered questionnaires?

DR. MUENZ: No, they're not self-administered, but some people simply did not give an answer. They -- the surgeon would ask him a question, and they did not respond. They were gently prodded to provide a response and did not do so.

DR. BOYKIN: Are you censoring that data or what?

DR. MUENZ: This isn't a time to event analysis. So the issue of censoring doesn't arise, but, yes, in the time to event analysis, there is censorship.

DR. BOYKIN: The problem is how do you

correlate some of these problems if you are going to selective, or not you, but if the patients don't choose to answer all of the questions or if we can't have that information, then we have to move these patients out of that population.

I mean if there's some relationship between change in nipple sensitivity and inflammation or asymmetry, we don't learn that.

DR. MUENZ: Well, this is the same issue that Dr. Blumenstein was referring to this morning. This is this issue of informative censoring, and there may, in fact, be a modest amount of informative censoring. I have no impression that there's a great deal of it.

For example, in another analysis that -- a more technical, fancier analysis that we're not looking at at the moment, I asked whether number of attended visits relative to the total number of scheduled visits predicated the quality of life outcome. That's an example of an analysis where I could take this issue of compliance into account, and I found that it did not.

DR. BOYKIN: Well, go to your next slide. I think I've written this down in sequence.

Okay. That group had 12 months. Your denominators are 45 and eight.

DR. MUENZ: Yes.

DR. BOYKIN: Which is a total of 53, and the slide before that your denominators total 64. So you lost 11 patients, and with the numbers that you're looking at, that carries a significant power of relevance for statistical imaging. Am I wrong with that?

This is the concern to the number of patients that you're looking at. I mean if that was 245 and 208 and you missed five or ten and numbers like that, that's one thing, but for such a small sample to have an 11 patient difference between these gives me a -- I'm not very comfortable if we begin to talk about what relates to what, and that's my concern.

DR. MUENZ: Well, I understand the issue, and it is that issue of informative sensoring, and I only can respond that when I did analyses that --

because I don't know what these people would have responded had they showed up, and of course, that is the issue.

When I asked the question is there a relationship between some of the outcomes and compliance, I found no evidence of such a relation. That is, I found no evidence that people who were dissatisfied tended not to come back or only those who were particularly satisfied tended to return.

But, yes, in fact, it is true that some people did not respond at a particular moment, and then I have neither a numerator or denominator for them. It would be inappropriate to impute the worst possible result for those people and that is not the analysis that I did.

Is there another statistical issue regarding this particular topic?

DR. BLUMENSTEIN: Well, but in fact, and in the presentation of the French data, that is exactly what was done, was the denominator was the whole group as opposed to whittling the denominator according to response.

DR. MUENZ: That's right, and I think that pessimistic kind of an imputation, imputing the worst possible result, gives an overly pessimistic perspective as to what's happening.

If we could answer please one.

DR. O'LEARY: I'm Dr. Pat O'Leary. I was wondering if we could respond to Dr. Burkhardt's question again.

If you remember back when those implants came out that had the high rupture rate, you remember that they were very thin shelled. They had approximately a 100 percent rupture, and I mean even after six months, most of those were taken out.

That was a different manufacturer and has absolutely nothing to do with PIP implant. PIP learned from that experience and has modified the implants.

The question was asked what the shell thickness is. It's .37 to .63 with a median of .5 for the smooth and .63 to .95 with a median of .7 millimeters for the textured.

DR. LI: I'm sorry. What units are you

using?

DR. O'LEARY: Pardon?

DR. LI: What units are you using?

DR. O'LEARY: Those are millimeters.

DR. LI: Sorry. So could you go through one more time?

DR. O'LEARY: Point, three, seven to .63 for the smooth; .63 to .95 for the textured.

I'd like to give you a little bit of history on the other. Dr. Burkhardt will remember when those implants came out, it was commonly thought that the shell contributed to capsular contracture. So the manufacturers were trying to make a thinner and thinner shell, and that's what led to that rupture.

So what we've done now is we've gone back and we've thickened the shell up and strengthened it so that we don't have those kind of ruptures, which is demonstrated in the clinical studies of which you can see the rupture rate is 5.3 percent in the sample. After two years the French study was approximately 2.1 percent, and the MDRs is less than 1.5 percent rupture.

DR. BURKHARDT: Obviously we'll have to rely on the data provided, to the extent that we can. I think for the general information of the panel, you should know that my concern is based on what plastic surgeons were told at that time, which was that the platinum cured devices were harder; that the composition of the material was harder. It was more likely to be abraded for that reason, and that this was the reason for the high incidence of leakage.

And I don't want to tar you with somebody else's brush, but this is going to be a major marketing problem for your product as I'm sure you realize.

MR. O'LEARY: Yes.

CHAIRMAN WHALEN: Dr. Li.

DR. LI: Just maybe for Dr. Burkhardt, I quickly translated the thinnest number that you provided, and that's .015 inches, which was essentially the thinnest possibility in the last two submissions.

DR. BURKHARDT: That's good.

DR. LI: Was this thickness range in the

PMA, by any chance? Because I was unable to find it.

PARTICIPANT: I'm sorry. What?

DR. LI: Were these thickness ranges, were they provided in the PMA? Because the FDA reviewers and I couldn't find them.

MR. HAWK: Yes, they were.

DR. BIGGS: They've asked me to answer Dr. Burkhardt's question. My name is Tom Biggs, and I'm from Houston, and I'll say a few words to you again in a minutes.

But it's my impression that this implant is a much softer implant than the one that was used before, and it is a platinum cured implant, and it has a better elongation capacity than what's being used today in the other implants, and it's much sturdier than what was used in years past.

And in a few minutes I'll give my own personal experience, but this has not been a problem. This immediate leakage/rupture has not been a problem.

DR. BURKHARDT: Thank you.

DR. LI: I'm sorry. I hate to be compulsive about this, but can we move away from I

think it was softer/harder and give me some numbers.

(Laughter.)

DR. LI: I mean if it was thinner, how much thinner for those of us that weren't around at that time? And if the other one is softer or yours is softer, can you give me some numbers?

DR. O'LEARY: That was not our implant, and I'm just going by hearsay that it was approximately about 5/1000 of an inch.

DR. LI: If it's hearsay, that's fair enough. I just couldn't -- I mean everybody was saying as if it were fact and nodding, and I had no idea what you guys were --

DR. O'LEARY: In fact it's thinner. How much thinner and exactly what the range was, et cetera, I'm not sure, but I --

DR. LI: How about the softness/hardness thing?

DR. O'LEARY: Softness/hardness? He's a plastic surgeon. They do the softness/hardness.

(Laughter.)

PARTICIPANT: It's softer.

DR. CARABIN: If I may be allowed to finish answering Dr. Chang's question. We've evaluated our explantations. They're a total of seven, and we identified one patient as having folds or wrinkles as the reason for the explanation.

DR. CHANG: And other than that, did you have any reason for failure? Was it --

DR. CARABIN: The other explanations?

DR. CHANG: Un-huh.

DR. CARABIN: There were deflations and infection, although the one case of explantation due to presumed infection, no culture grew any organisms at the time of explantation.

DR. CHANG: So of the implants that you were able to get hold of --

DR. CARABIN: Yes, ma'am.

DR. CHANG: -- after they were implanted, how many were due to implant failure, not infection or, you know, pieced by needles, but --

DR. CARABIN: Well, deflation certainly is hard to determine if it was due to puncturing at the time of surgery or if it was puncturing at the time of

exchange of the implant. That's always an iffy question.

DR. CHANG: But one out of seven had a wrinkle.

DR. CARABIN: One out of seven had a wrinkle, correct.

CHAIRMAN WHALEN: I see no other questions. Were there any of the panel's questions that they feel are lingering? I may have lost one in the unsync of the answers.

No, then I'd like to thank --

MS. DUBLER: I have one.

CHAIRMAN WHALEN: Ms. Dubler.

MS. DUBLER: Just one, and I'm not sure I can either ask this question intelligently or understand an answer, but on many of the slides it said "noncumulative point relevance." Can you tell me what that means?

DR. MUENZ: Yes.

MS. DUBLER: In simple concepts that I can grasp.

DR. MUENZ: How many people have the thing

at that moment. It's the fraction of people who have got the particular finding at the moment. Take a slice in time, ask how many people. If you have 100 people and three of them have it, then it's three percent. If you have 50 people and ten of them have it, then it's 20 percent. So that's all it is. It's just the proportion of people with the particular phenomenon at that moment.

MS. DUBLER: So when you had three, six, and 12 months and the percentages at each of those would reflect the slice in time, not a percentage of your whole N.

DR. MUENZ: They reflect the people who were available who answered the question at that moment.

MS. DUBLER: I see. Thank you.

DR. CARABIN: If we can be permitted --

DR. MUENZ: There's another flavor of that thing called cumulative, which counts everybody who's ever had the event, and we also have that. The FDA guideline -- the FDA produced a guideline document which said what are you supposed to tabulate, and

there's two main flavors of these kinds of epidemiologic tabulation.

One is the noncumulative. That's the single slice in time asking what fraction of people have it at this moment, and then there's a cumulative which counts whoever had it ever, and in principle that can only go up because if you've ever had it, it can't go away.

CHAIRMAN WHALEN: I see that there are no further questions. Dr. Burkhardt and Dr. Li, you're satisfied in terms of thicknesses, platinum curing, and that entire topic or --

DR. LI: I guess as far as questions. I have lots of comments, but perhaps not for discussion.

CHAIRMAN WHALEN: There will be time for that.

You're okay, Dr. Burkhardt?

Then I thank the sponsor.

We need to go somewhat out of sequence I'm told, and have now before FDA's presentation the second open public hearing.

All persons who are addressing the panel

-- and I thank the sponsor, and it's fine to vacate that table. Sorry -- all persons addressing the panel should speak clearly into the microphone as the transcriptionist is dependent on this means of providing an accurate record of this meeting.

I'm getting sick of saying this actually. It reminds me of Robin Williams saying, "Look in the dictionary at the word 'redundant,' and it says 'see "redundant."'"

(Laughter.)

CHAIRMAN WHALEN: The instructions from this morning still apply. Remember we would ask that you disclose if anyone is paying for your trip or accommodations, if you have any financial ties to industry or health professional societies.

We would also have you disclose whether you are a witness or party to any lawsuits related to breast implants or whether you derive any of your income from medical procedures involving breast implants or symptoms attributed to breast implants.

There was one previously identified speaker who will go first, two people who have asked

today to speak who will go second and third, and then if there is additional time, I will open it to any other individuals who wish to speak.

The first to speak to us is Ms. Roberta Glick.

Ms. Glick is not present apparently.

Next is Ms. Diana Zuckerman. All right. Then Cindy Pearson is going to go first and then Diana Zuckerman.

MS. PEARSON: Thank you.

I'm Cynthia Pearson, Executive Director of the National Women's Health Network. My answer to all four disclosure questions is no.

I wanted to thank the panel for giving us the opportunity to speak at a time in which we can respond to the data. You all remember that I spoke yesterday morning with general comments on the subject, but as a consumer group using a science base to make an analysis of the pros and cons of various choices in women's health, we're very interested in the data, and we appreciate the chance to share our reactions at this point in the conversation when they

might be able to be interwoven into your further discussion and questions.

And it seems at this point that what the sponsor of this particular product has been able to show you is that there is a relatively low chance -- they have fairly decent scientific evidence that there's a relatively low chance of a significant clinical problem happening within two years if you go to France and see one of six surgeons.

And I think that is a step in the right direction. It is some good evidence of relatively low complication rates documented through a scientific process. It doesn't seem that they've gotten that far with their U.S. study, nor does it seem that they have plans to go beyond two years.

So from a consumer perspective, at this point it doesn't seem like any woman in the United States who is not going to go to France and see one of those six surgeons would be assured that the reasonably decent evidence of low complication rates at two years would apply to her in this country with the variety of surgical techniques here.

And no woman anywhere would be assured from evidence developed through a scientific process that she would have long term assurance.

And so in the possibility that you may way this device, this particular device isn't ready to be approved yet, I'd also like to comment on what would consumers like to see in data, and I will reflect a little bit on the questions that troubled you this morning.

Because it seems that we agree with you that you believe that women -- it isn't helpful to women to be told there's a 90-plus complication rate when complication has been defined to include things that are planned and expected.

So we agree that particularly for reconstruction patients, when you ask for data from this device if it comes back again or if other devices are in development that come, that the most useful information is what are the unexpected and adverse events and what is the likelihood, and hopefully over a period longer than two years.

I would say though that as you seem to

struggle with what is the correct number, what's the informative number to share with a woman considering these devices in terms of augmentation where she doesn't have the issue of automatically and almost always planning another procedure, that it is reasonable to share with women a global number of all adverse events, whether or not from a surgeon's perspective some of the events were elective and patient choice.

From a surgeon's perspective, it may seem as if why should we bear the complication rate for someone who decides she wanted to change her size after one surgery has already taken place, but from a patient's perspective, I don't think any woman goes into an augmentation procedure planning to have another one. She wants the first one to work.

And it's sort of like the feedback that the consumers gave in vitro clinics in the early days of in vitro, and to a specialist in that world the important piece of information they could share was how well does this new technique work. How well does our new found ability to take a fertilized egg from

the test tube, put it into a woman's body, and get an implantation and a positive pregnancy test? What's your percent likelihood of that? What's our percent likelihood that we've developed this new technique.

But for the woman going to the infertility clinic, the important information for her was how likely was she to have a baby, and similarly, I would share with you that as you consider, you know, devices in the future where you've got more mature data and more data, that you keep in all adverse events in the calculation of how likely is a woman to experience some complication or an adverse event.

And if it is as ugly as these morning data were, 60 percent at four years, 68 percent at five years for patients with augmentation, I would challenge you to rethink whether that's really acceptable safety in terms of how likely is a planned procedure to work without needing to -- without causing complications or additional procedures.

And those are our comments, and thank you for the time.

CHAIRMAN WHALEN: Thank you.

Diana Zuckerman, please.

DR. ZUCKERMAN: I'm Diana Zuckerman. I'm the Director of the National Center for Policy Research for Women and Families still, as I was yesterday, and I'm still donating my time to be here, and the answer to the other questions is still no.

I actually want to start out by thanking all of you for spending three days doing this because I really do recognize what a stress and strain it is on all of you, and you all might wonder why some of us are spending three days here as well.

I just want to address that briefly. I started out as an academic researcher doing epidemiology research, and in one of my early jobs in the beginning of my career, I hired a research assistant, who was really a terrific guy. He was smart and dedicated and worked very hard, and he had no arms. He was a thalidomide baby,a nd it was a very early reminder to me of the importance of the FDA, an agency I knew nothing about really at the time when I was in academia.

You know, I think thalidomide was one of

the finest moments of FDA where scientists at FDA determined that a product had not been proven safe and really resisted a lot of pressure to keep it off the market, not because they had evidence at that time that it caused birth defects, but because there was no evidence that it was truly safe.

And so not to get overly dramatic about it, but people do really rely on FDA to make sure that products are safe. We really do look to FDA and look to these panels that a determination that a product is safe actually means something.

And it's difficult when you have data that's problematic in a variety of ways, and so yesterday you started out with some data with some rather high loss rate, loss of patients over time. That's a problem, and a high rate of complications.

And then today, this morning, you had some studies with an even higher dropout rate and even higher complications, made even more difficult because complications were defined in a way that in some cases really did not make sense.

And I agree that there's certain

complications that are not complications. If they were expected ahead of time, you shouldn't count that as a complication.

Now you're being asked to look at some data that has an even higher dropout rate of people not completing follow-up, a smaller sample, much smaller, and what do you do with that?

And I guess what I'm asking for is that FDA hold onto a standard that really makes sense to consumers so that when you determine that a product is proven safe or even reasonably safe, that consumers really believe that that means something, that you really have looked at data that makes sense to you that you can understand because it's clear, that has implications for real people out there whose lives are depending on you, and so that they know when you say that you think something's safe, that they can feel confident that it really is safe.

Thank you.

CHAIRMAN WHALEN: Are there any other members of the public who wish to address the panel? If so, would you please identify yourself with the

other stipulations that we have requested?

(Pause in proceedings.)

CHAIRMAN WHALEN: Realizing the evils of technology, we do need to have you proceed because --

DR. BIGGS: All right. Ladies and gentlemen of the panel --

CHAIRMAN WHALEN: -- with a maximum of five minutes.

DR. BIGGS: -- my name is Tom Biggs, and I'm from Houston, and I am a clinical professor of plastic surgery at Baylor in Houston, and I am formerly the President of the Houston Society of Plastic Surgeons, the Texas Society of Plastic Surgeons. I am the Chairman of National Secretaries for the International Society of Aesthetic Plastic Surgery. I'm a former visiting professor for the International Society, and I'm currently the visiting professor for the American Society of Aesthetic Plastic Surgery.

I don't think Ms. Zuckerman was comparing the --

CHAIRMAN WHALEN: Sir, your full

disclosure relationship to the --

DR. BIGGS: Oh, yes. My expenses for being here have been paid for by PIP. I have no other contractual relationship with the organization, nor do I own stock in it.

I gain some of my income through the treatment of the breast with breast implants, and I do, like many other plastic surgeons in Texas, have some pending lawsuit having to do with litigation against the manufacturers.

I'm here to talk to you about breast implants though. In my group, we've got over 8,500 cases, and I'm responsible for probably two thirds or more of those. So I have an experience with breast implants.

My original relationship was with a man named Thomas Cronin, who was clinical professor of plastic surgery at Baylor, and Dr. Cronin in 1962 put the first silicone breast implant into a human being in Houston, Texas at Jefferson Davis Hospital, and I was his resident. I was with him in the room that day.

This is a picture of the very first implant with the dacron back.

Now, I was with Dr. Cronin after that and his partner for 20 years, and we went through the entire evolution of breast implants, and I think we've used virtually every breast implant that's been manufactured.

In 1963, Dr. Cronin went to the International Plastic Surgery meeting in Washington, D.C., and presented a new, natural feel prosthesis, and from that moment on there was a tremendous demand for breast implants.

I did a capsule study of the fibrous capsule around the implants with an electron microscope, and I found that in that capsule there was blood, blood particles, wood particles. There were cotton particles, and there was talc, and based on that study, I have determined that those components contributed to the capsular contracture problem.

And so from that moment on I made certain that we had an extremely bloodless field when we operated, and that we never put an implant onto a

paper drape because that's where it picked up wood particles onto the surface of the implant.

We never stuffed a cotton sponge or a lap pad inside the wound because we were imbedding cotton fibers into the space, and that contributed to inflammation and, thus, more capsule, and the talk on our gloves was certainly a factor in the development of capsular contracture.

So the capsular contracture phenomenon has been minimized by technical changes that we have exercised in the operating room.

Now, we certainly have gotten some lovely results with breast augmentation through all of the evolution of the implants, but because of the history during the last decade, we now use silicone implants filled with saline.

Now, these silicone implants are bags with a fill tube, and we instill the saline through this fill tube into the bag, thus inflating it to its maximum capacity.

Now, these silicone implants filled with the saline were a bit firmer than the gel, and the

fill tube was a bit of a burden because we had to put the fill tube in. We had to take the air out, and it took some time in the operating room to do that.

And likewise, there was a certain deflation rate. Now, I through the exercise of rather careful operative techniques, we were able to have relatively good results of these implants, and I am not displeased at all with the saline filled implants that I was using prior to the introduction of the PIP.

However, with the PIP I had some other observations. It was introduced to me as a good implant and being used in France very successfully, and so I consulted with several of my French colleagues, and they said, "Yes, absolutely," that they had been using it for several years, and they had excellent results with it.

So based on that, I began using it, and it comes packaged very carefully in several packages, and I am the one -- those are my hands -- I am the one that opens the first package and the second package and the third package and takes the implant out. No one touches the implant but me.

And since I don't lay the implant on the cotton drapes or on the paper drapes, this is a no touch technique. So referable to comments that were made yesterday and some this morning, there's a technical aspect to this operation, as well, and this is something that I teach my residents: how to put this implant in without exposing it to a lot of other factors.

Now, this is the implant that I'm holding. It's a soft implant, and it's soft because the shell has a greater elongation capacity, and this is one of its great, great assets and benefits.

Now, on the left is a picture of me holding a silicone gel implant, and on the right a picture of me holding a PIP saline filled implant, and as you can see, they look almost the same, and truly they feel almost the same.

So because of the softness, I was pleased to begin using the PIP implant, and I've gotten some lovely results with it.

The PIP implant in my experience, and these are not data I'm presenting you. This is just

my experience and my observations over the last two years, is that I've had 65 patients, and 64 have been satisfied.

One is not satisfied because she has some significant asymmetry, and I think part of that was my fault technically, but truly 64 have of them have been satisfied.

And I've put in 133 implants, and I've gotten no infections of any sort and I've had two deflations, and I think both of those deflations were technical as well because they occurred within the first few weeks. They were noticed within the first few weeks after surgery, and there was a tiny pinhole right at the side of closure of the wound. So I don't think they were fold flaw problems.

We had no hematomas, and we had one case of asymmetry. That's that dissatisfied patient, and the contracture rate, Baker's III and IV, was zero, and I think the contracture rate, Baker II, in a thin patient is fairly normal.

CHAIRMAN WHALEN: Doctor, excuse me. The timer was involved in audio visuals and may not have

been able to set things rightly, but you've been over five minutes, and I'll have to ask you --

DR. BIGGS: May I have 30 seconds more?

CHAIRMAN WHALEN: If you'd conclude quickly.

DR. BIGGS: Why do I use an implant? Because there's no valve to leak, prefilled, yields shorter operating time, less danger of contamination, and it's softer, and patient satisfaction is very high.

Now, we need implants. I like the PIP because it's aesthetically desirable. It's effective, and I think it's safe.

Thank you very much.

CHAIRMAN WHALEN: Thank you.

We will now take a ten minute break at the end of which FDA will begin their presentation.

(Whereupon, the foregoing matter went off the record at 3:57 p.m. and went back on the record at 4:09 p.m.)

DR. HUDSON: Good afternoon, members of the panel, ladies and gentlemen. I'm Peter Hudson,

the lead reviewer of Poly Implant Prostheses prefilled saline breast implant PMA.

I'll be presenting a summary review of the preclinical and clinical information. Ms. Judy Chen will then present the statistical review of the information.

Poly Implant Protheses, or PIP, gained market clearance for their saline breast implant in the United States via pre-market notification in 1996. PIP agreed to staged submissions of data on evaluations of the chemical, toxicological, mechanical, and clinical aspects of their device in 1996.

PIP submitted their PMA on November 17th, 1996 in response to FDA's final rule issued on August 19th, 19999. The subject device is a hemispherically shaped valveless, saline prefilled breast implant.

PIP offers four basic styles of implants: a smooth, low, or standard profile device; a smooth, high profile device; a textured low profile device; and a textured high profiled device. Each style is available in a range of volumes. The implant is

prefilled with physiological saline.

The indications for use requested for PIP saline breast implants are cosmetic breast augmentation, unilateral or bilateral undeveloped breasts, revision surgery. PIP is not requesting approval for the indication of reconstruction.

The preclinical information is broken into three sections: chemistry, toxicology, or biocompatibility, and mechanical testing.

FDA considers all of the chemistry analyses conducted to date to be incomplete. A deficiency letter has been spent to the sponsor. Without complete chemical analysis we feel that no conclusions can be drawn about the chemical aspects of this product.

Question one of FDA's questions to the panel requests panel commentary on the importance of these tests when evaluating the safety and effectiveness of the device. PIP has submitted an amendment to their PMA in response to FDA's deficiency letter. The amendment was received on February 26th.

The sponsor has conducted the recommended

list of biocompatibility tests on the sterilized final device with the following exceptions. Chronic toxicity and implantation evaluations of the device have not been conducted. The sponsor has a study in progress that will address both tests.

The sponsor has not evaluated the device in a carcinogenicity study. They have conducted bacterial mutagenesis in mammalian cell genotoxicity analyses, and they have initiated a carcinogenicity study.

PIP did not provide any information addressing pharmacokinetic analysis of leachable chemicals. These analyses are recommended by FDA to address the pharmacokinetic behavior of potentially toxic chemicals that might reach out from the device.

There is information in the scientific literature regarding the absorption, distribution, metabolism and excretion of cyloxane (phonetic) leachables. It is the sponsor's responsibility to determine the type of information to be provided.

These issues were addressed in FDA's deficiency letter to the manufacturer. Question one

of FDA's questions to the panel, in addition to addressing chemistry issues, requests panel commentary on the importance of these tests when evaluating the safety and effectiveness of the device.

The mechanical testing is not complete. Static rupture and fold flaw analyses were not addressed in the PMA. There is insufficient information present in the PMA to adequately characterize the mechanical properties of the device.

Question two of FDA's questions to the panel request panel commentary on the importance of these tests, as well. The amendment just submitted by PIP contains information regarding mechanical testing. The information has not been reviewed.

This slide summarizes the medical device reports that FDA has received for PIP, saline filled breast implants during the last three year period. The slide summarizes the most frequent problems reported to the MOD or manufacturer and user facility device experience database.

The database receives reports from patients, health care practitioners, and

manufacturers.

PIP has submitted clinical information from three different sources in support of their PMA. Information obtained by means of a survey sent to non-study surgeons who have implanted the device in patients since 1996 in the United States; data provided from PIP's discretionary post marketing surveillance study in the United States, and data obtained from PIP's clinical study conducted from 1995 to 1997 in France.

Questions three, four, and five of FDA's questions to the panel ask whether there is sufficient data to demonstrate a reasonable assurance that the product is safe and effective for augmentation and revision patients.

We will ask for your comments regarding the minimal duration of follow-up, the type of follow-up visit that is active or passive, and the types of complications that are important to assess. Please consider this as I go over the clinical information provided.

PIP initiated a retrospective survey of

U.S. surgeons to collect information on the surgeon's experience with PIP's saline breast implants. Patients who have been implanted for two years or more were identified by their medical device registration forms. A letter was sent to the implanting surgeons to request a surgeon's participation in a survey of the results obtained in these patients. A one page form was developed to use in reporting information on the implants. The form was to be completed by chart review and by conducting a short telephone interview with the patient.

The one page survey requests basic patient demographic information, implant type, and the indication for use, that is, augmentation, reconstruction, or revision. Patient satisfaction is assessed by a check box questions, and bra size preoperatively and postoperatively is recorded.

The following complications are provided as check box questions: calcification, infection, hematoma, leakage or rupture, nipple sensitivity, capsular contracture, Baker Grade III or IV, immediate postoperative complications, and other complications

requiring reoperation.

Implant related disorders or problems are provided as check box questions for autoimmune disorder, connective tissue disorder, pregnancy related issues, lactation problems, X-ray or mammogram problems, and other.

Since PIP began marketing their saline breast implants in the United States, 35,000 devices have been implanted in about 17,500 patients. Approximately 3,480 patients have been implanted for two more years. Fifteen surgeons who have implanted 1,257 patients agreed to participate in the survey. Information was provided on 777 patients, representing 22 percent of the patients with two year implant experience with the sponsor's device.

The majority of the patients that the information was provided for in the surgery were augmentation patients, 85 percent, 86 percent. Textured implants were more commonly chosen by the physician and patient.

The strengths of this survey are the number of augmentation patients implanted, and that

both textured and smooth devices were used.

The weaknesses of the data are that the information was collected by a retrospective survey of the patient's information. The fact that bias may have been introduced with only a subset of surgeons responding; that there is data only 73 revision patients; that the data represents only 22 percent of the patients who have reached two years in the United States, and that the data collected was obtained by chart review and telephone interview.

Now I'll discuss the clinical study conducted by PIP after clearance of the pre-market notification application in 1996. The U.S. discretionary post marketing surveillance study design calls for the inclusion of 1,000 women having breast implantation for the following indications: revision, reconstruction and augmentation.

Two hundred and 50 patients were to be enrolled as either revision or reconstruction, and 500 patients as augmentation patients. Patient follow-up visits were scheduled for three and six months, one and two years, and annually out to ten years

postoperatively.

Safety evaluations. Safety information is obtained from the follow-up assessments and includes the incidence of complications and the resolutions to complications, whether there were any pregnancy or lactation problems encountered and a detailed questionnaire regarding connective tissue disease.

Efficacy is assessed by quality of life questionnaires, the Rosenberg self-esteem questionnaire, the medical outcomes survey, and the body esteem scale questionnaire, and pre and postop breast size measurements.

It's important to note that this study was designed in consultation with the FDA. It has a statistical plan. In addition, the study collects detailed safety and effectiveness information.

It is the only source of clinical information submitted by PIP that attempts to address -- to assess the patient's quality of life using validated quality of life measurement instruments.

To date PIP has enrolled 393 patients among all three indications. Of the 393 patients

enrolled, 332, or 85 percent of the patients were implanted for augmentation purposes, and 60 or 15 percent were implanted for revision purposes. One patient was enrolled with the indication of reconstruction.

Remember 500 patients were proposed to be studied in the augmentation cohort, and 250 patients were proposed for both the reconstruction and revision cohorts. Remember also that the sponsor is not pursuing the indication of reconstruction.

Thirty-five percent of patients in the total population were implanted with textured devices, and 62 percent were implanted with smooth devices. This same ratio that is approximately 35 to 65 percent is observed for textured and smooth devices when stratified by indication.

Age, income, marital status, and education are not available in the study database. The only available demographic feature is race. Of the primary augmentation cohort, 84 percent are Caucasian, seven percent are Hispanic, seven percent are Asian, and two percent are African American.

In the revision cohort, the percentages are 96 percent. It's overwhelmingly Caucasian, two percent Hispanic, two percent Asian.

Of the 392 patients enrolled for augmentation or revision, there is safety and efficacy information for 27 percent of the respective individual cohorts at one year. That is, of the 198 augmentation patients due at one year, data was provided for 54 patients, or 27 percent of the augmentation cohort.

Of the 37 revision patients due at one year, data was provided for ten patients or 27 percent of the revision cohort.

At one year, 20 percent of augmentation patients and revision patients had a complication, any complication. For the augmentation cohort, 20 percent represents 11 patients of 54 evaluated.

For the revision cohort, 20 percent represents two of ten patients evaluated.

Capsular contracture of Grade II or higher -- the sponsor has provided information that only Grade II is noted in these patients -- was eight

percent, and leakage and deflation was two percent for each.

Seven patients of the augmentation and revision patient populations have had devices explanted, or 11 percent of the combined augmentation and revision cohorts by one year. The sponsor has not provided any information on the reasons for explantation, at least not in the PMA up to this amendment that we just received.

Twenty-seven percent of augmentation patients reported asymmetry by one year. The valveless design may influence the ability to achieve a symmetrical outcome. The volume cannot be adjusted to compensate for natural anatomic asymmetry.

Forty-one percent of augmentation patients and 50 percent of revision patients reported a change in nipple sensitivity by one year. The number of evaluated patients are low, but the incidence for these complications appears higher than expected.

Question eight of FDA's questions to the panel ask for your comment as to whether there should be any specific labeling regarding asymmetry or

changes in nipple sensitivity. PIP has provided data in their presentation on pregnancy and lactation difficulty. However, it's not known whether any patients were pregnant or lactating during this period of follow-up.

The sponsor has been requested to provide information on the causes of reoperations, as well as the number of end results of patients who had mammographic examinations.

The sponsor collected quality of life data using the Rosenberg self-esteem scale, the medical outcome sale, and the body esteem scale. The data demonstrated that there was a worsening of the Rosenberg self-esteem score, the current health perception subscale, the medical outcome scale, and the physical condition score subscale of the body esteem scale at three months.

However, there was an increase in the perceived sexual attractiveness subscale and body esteem scale at three and six months. The data, again, is influenced by poor follow-up and by the low numbers of patients enrolled. The sponsor also

collected data on post implant cup size. The conclusions of this information was similarly hampered by poor follow-up and by the low numbers of patients enrolled.

In summary, the strengths of this clinical data are that the data was collected prospectively. The proposed enrollment was for 1,000 patients. The patients were followed for complications and assessed with a detailed connective tissue disease questionnaire. The patients were evaluated for effectiveness by quality of life and bust size measurements.

The weaknesses of the study are that only 393 total patients have been enrolled, 332 augmentation patients, 60 revision patients, and one reconstruction patient. At one year safety data has been collected on 54 augmentation patients and ten revision patients. This represents 27 percent of the number of patients enrolled for either cohort, and 6.4 percent of the number of patients proposed as being necessary to demonstrate safety and effectiveness in the original protocol design.

There is no safety data beyond one year, and the effectiveness data is based on the data collected at the patient's last visit, which is primarily three months data.

Now I'll review the French clinical study. PIP conducted a clinical study of the breast implant, their breast implant, between the years of 1995 and 1997 in France. The indications for the use of the device in the study were augmentation, reconstruction after mastectomy, and reoperation. Patients were assessed at follow-up visits at six months, one and two years. Textured implants only were used in the study.

Safety information was obtained from the follow-up assessments and included recording complications. Noted omissions from the list of complications assessed were reasons for explantation. Information pertaining to how complications were resolved, a detailed assessment of connective tissue disease, and an assessment of pregnancy or lactation related difficulties.

No objective efficacy endpoints were

assessed in the study. Question six of FDA's questions to the panel requests comment on the lack of information of the French clinical study regarding interference in mammography or lactation.

Of the 521 patients enrolled in the French clinical study, 78 percent were augmentation; 16.5 percent were reconstruction; and 5.5 percent were revision patients.

Of the patients enrolled in the study, PIP collected safety data on 82 percent of the patients at two years. Of the total number of patients expected for the augmentation and revision cohorts, or 435 patients, the sponsor had follow-up information on 84 percent or 366 patients at two years. No demographics were provided for the study population.

Again, I'll remind you that PIP is not pursuing the indication of reconstruction.

The incidence of rupture at two years for augmentation patients was two percent with confidence limits indicating a range of potential rates of 0.5 to 3.4 percent. Three, point, seven percent of augmentation patients were explanted by two years with

the confidence interval indicating that the incidence could be as low as 1.7 percent and as high as 5.6 percent.

For revision patients, the rate for rupture was 7.7 percent with a range from zero to 22 percent. The broad range for revision patients was due to the low number of patients evaluated. Seven, point, seven percent reflects a report of one case of rupture of the 13 patients evaluated.

Two patients in the revision cohort were explanted by two years, resulting in a 15.4 percent incidence of explantation in that patient population. The confidence intervals for revision patients who are explanted or who had capsular contracture of Grade II was broad, indicating that 35 percent of revision patients might require explantation within two years, and that as high as 22 percent of revision patients might experience capsular contracture of Grade II by two years.

PIP has not provided the reasons for explantation.

PIP reported the incidence of capsular

contracture, Grades II and III as higher, as recommended in the guidance document. The rate for capsular contracture, Grade II and III and higher, for augmentation patients is 2.6 and 1.4 percent, respectively at two years.

A very low infection rate was reported for the augmentation patients, 0.3 percent or one patient in 353 total evaluated.

Of the revision patients evaluated at two years, only one patient had capsular contracture of Grade II or higher, resulting in a 7.7 percent incidence. Again, the confidence interval is broad with low patient numbers.

The sponsor's case report forms collected information regarding asymmetry, a change in nipple sensitivity, and breast pain, but we had not received any information in the PMA. There might have been information regarding these complications in the most recent amendment.

In summary, the strengths of the French clinical study are that follow-up was obtained on 82 percent of the total enrolled patients, which included

the indications of augmentation, revision, and reconstruction.

The augmentation cohort consists of 353 patients at two years. The weaknesses of the study are that patients only received textured implants, and the sponsor proposes approval of both smooth and textured implants.

Two year data was provided on only 13 revision patients. No effectiveness data on quality of life or bust size was collected, and there is no information on reoperations and no data on patients who were explanted.

This slide summarizes PIP's clinical data. Data was collected from three sources: the U.S. surgeon's survey, the DPS study, and the French clinical study.

The U.S. surgeon's survey was a retrospective survey of data obtained from chart review and telephone interview on 666 augmentation patients and 73 revision patients, representing only 22 percent of the patients implanted in the U.S. with two year implant experience. Data from the

prospective DPS study was available at one year on 54 augmentation patients and ten revision patients, representing 27 percent of the enrolled patients and 6.4 percent of the proposed number of study patients.

Data from the French clinical study was based on two year follow-up of 353 augmentation patients and 13 revision patients representing 87 percent, and 45 percent represent follow-up with respect to cohort.

All patients received textured implant, and the study had no objective efficacy on points identified.

Question 7 of FDA's questions to the panel was a general question regarding sexual -- surgical practices. Excuse me.

(Laughter.)

DR. HUDSON: And postoperative management of mammary implantation.

We'd appreciate your comments and discussion on these.

I will now introduce Ms. Judy Chen, who will provide the statistical review. Thanks for your

attention.

MS. CHEN: I'm Judy Chen, the reviewing statistician for this submission.

This submission included three studies: the post marketing surveillance study, which is a UA study, and a French clinical study, and then a surgeon case experience.

Due to the obvious limitation of case experience, I will only comment on the first two studies.

For the post marketing surveillance study, there is a protocol, and the protocol indicated that this is a post marketing follow-up patient at three, six, 12, and the 24 months post implantation and even for -- there is even maybe longer follow-up data.

And there will be a clinical monitor to assure the complete and accurate data collection. As also indicated, there will be 1,000 patients planned, and there was approximately 20 percent revision, 20 percent reconstruction, and 60 percent augmentation patients.

This is what the results that we have are.

Among the 392 implanted patients, there was 357 who are due for three month follow-up, which had enough follow-up time, and there are 306, 306 patients who are due for six months, and 235 patients who are due for 12 months. So you can see the patient difference between the three and the six months. These patients can be considered as censored.

But more importantly, that at three months or at any time, not all due patients are evaluated. Even at three months, out 357 patients there are only 166 evaluated. At six months, out of 306 patients there are only 101 evaluated. At 12 months, out of 235 patients, there are only 64 patients evaluated.

And not all evaluated patients have data every event, every kind of endpoint. For rupture, out of 166 at three months there are 132 patients at risk, meaning have data on that particular endpoint, and so on.

This slide pretty much shows you how much data we have. Not only there is a problem with the sample size. With this amount of missing data, potential bias is a very serious problem.

The safety was evaluated by us as to all occurrence and all known occurrence and also as presence or known presence of adverse events at fixed time point. This is where we're talking about an incidence and the prevalence.

However, this method is not very useful since it's only relevant for even three patients at fixed time points. I have just shown in previous slides only a very limited proportion of patients that have follow-up, for example, at one year, and not all information are utilized.

Safety can also be evaluated by survival analysis using Kaplan-Meier estimate. This is a better method. It is relevant to the entire study population with data, of course, and all information are utilized.

And also this method allows -- censoring is allowed. The patient who didn't have complete follow-up are allowed with this method. However, if we assume time to the event is assumed to be independent of censoring time and other adverse events, here are some examples of the adverse event

rates according to survival analysis.

And I will just show this slide to you. This rate is very different from the previous rate. The previous rate is only relevant to the specific time point.

And I also like to point out to you by 365 days the number of patients already vary not large. By 450 days, the number will be even smaller.

This one shows revision patients, and this at the end was based on very small number of patients, especially the estimate at 450 days. The confidence interval, as you can see, are identical with the 365 days. Yet in all probability the number of patients has been decreased because of the longer time. So that upper confidence interval probably is not very good estimate.

These are the numbers for augmentation patients. Here is the comments for the post marketing surveillance study. First, insufficient study size. Only 392 patients were included, but 1,000 patients were specified in the protocol.

And also very seriously was high

proportion of missing data.

A third point is that even time may not be independent of censor time and other adverse events time. This is what we're talking about this morning.

Now we come to the second study, the French clinical study. In the submission, there's no protocol, clear protocol, included for this study, but there is description. PRP has indicated that they have also conducted a clinical study in France using a similar protocol and forms for capturing patient data, complications and other safety concerns. The number of patients entered was 521.

And this is the follow-up situation with the French study. As you can see, it's very, very different from the U.S. study; that at six months, patients due for six months follow-up are 521. That's 100 percent off what the patients who were independent. At the 12 months, it's 474, and at 24 months, it's 427.

But all of these patients, each and every one of them are evaluated, and also each and every one of them has data on every endpoint.

This is the adverse event rates that's estimated by the sponsor in the original submission. I understand that later the denominator has been adjusted to 427, but sine this is not using the survival analysis, neither of those denominators are an appropriate one.

I think there's a comment. Oops. There should be a comment. That's not the last one.

Okay. Now, here are comments for the French study. First, there's no protocol.

The second one, the results may be biased, first, because censoring is not appropriately adjusted.

And also I question the 100 percent follow-up of theoretically due patient, and also all patients have data for all complications.

Further there are 22 explanted patients. These patients are not addressed for the entire two years. Yet they are included in the denominator.

And the last one, the numerator might also can be inflated if there are under reporting.

This completes my presentation, and I

return it to Peter.

DR. HUDSON: Mr. Rick Hawk wanted to make a comment, and I can --

CHAIRMAN WHALEN: There will be a period of time the sponsor can comment later, but not at this juncture.

DR. HUDSON: I just want to clarify that the clinical protocol that was provide in the French -- for the French study, there was a protocol provided. It was very limited. It's not very similar in detail to their DPS study, but there is a protocol there.

Do we want to go --

CHAIRMAN WHALEN: That concludes FDA's presentation?

DR. HUDSON: Yeah.

CHAIRMAN WHALEN: Are there any questions of the FDA?

DR. BURKHARDT: I have a question.

CHAIRMAN WHALEN: Dr. Burkhardt.

DR. BURKHARDT: I'm sure this is very simple to the statisticians, but I don't quite

understand the due and evaluated meanings here. Why are the differences in the numbers 521, 474, 427? I don't understand what those numbers mean. Why do you have 521 patients due for follow-up at six months, on 474 at 12 months, and 427 for two years?

I'm sure it's simple, but I just don't understand it.

DR. HUDSON: That's just recently been clarified. In the initial report, they had -- 521 is total enrolled, and then the numbers decreased over time and listed as theoretically due. Those were -- and then they'd say they listed those numbers as being evaluated and, therefore, 100 percent followed up, but those are patients that they had missing data for and were not evaluated at those time points. So those would be considered lost to follow-up.

DR. MUENZ: May I respond to that? People enter over the course of time, and if everyone entered on the same day, say, January 1st, 1997, then it would be true at a subsequent moment that the number of people who were due for a given visit would always be constant.